# **Guidance for Industry**

## Charging for Investigational Drugs Under an IND — Qs & As

## DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Colleen Locicero at 301-796-2270, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013 Procedural

# **Guidance for Industry**

# Charging for Investigational Drugs Under an IND — Qs & As

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## **Guidance for Industry**<sup>1</sup>

## Charging for Investigational Drugs Under an IND

Qs & As

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### I. INTRODUCTION

This draft guidance is intended to provide information for industry, researchers, and physicians about the implementation of FDA's regulation on charging for investigational drugs under an Investigational New Drug Application (IND) (21 CFR 312.8), which went into effect on October 13, 2009. Since 2009, FDA has received a number of questions concerning its implementation of the charging regulation. As a result, FDA is providing guidance in a question and answer (Q&A) format, addressing the most frequently asked questions. In separate draft guidance, FDA is providing its thinking on questions concerning its implementation of its regulations on expanded access to investigational drugs for treatment use (21 CFR part 312, subpart I). Information concerning charging for investigational drugs made available under expanded access programs is provided in this draft guidance. Otherwise, information related to implementation of the expanded access regulations is provided in the expanded access draft guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

#### II. BACKGROUND

<sup>&</sup>lt;sup>1</sup> This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>&</sup>lt;sup>2</sup> 74 FR 40872, August 13, 2009.

<sup>&</sup>lt;sup>3</sup> Once finalized, the draft guidance on Expanded Access to Investigational Drugs For Treatment Use -- Qs & As will represent the Agency's current thinking on this topic. The draft guidance is available on the Internet at <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm</a>. We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page.

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For many years, FDA authorized charging for an investigational drug under a regulation that was published in 1987 (the 1987 charging rule) (52 FR 19466, May 22, 1987). In 2009, FDA revised its 1987 charging rule for three principal reasons: (1) to take into account circumstances concerning charging for investigational drugs in a clinical trial that were not anticipated when the rule was written; (2) to set forth criteria for charging for investigational drugs made available under all three categories of expanded access described in the expanded access regulations that were also revised in 2009, and; (3) to specify the types of costs that can be recovered when

The revised charging regulation provides the following:

charging for an investigational drug under an IND.

- General criteria for authorizing charging for an investigational drug (21 CFR 312.8(a))
- Criteria for charging for an investigational drug in a clinical trial (21 CFR 312.8(b))
  - Criteria for charging for an investigational drug for an expanded access use under 21 CFR part 312, subpart I (21 CFR 312.8(c))
  - Criteria for determining what costs can be recovered when charging for an investigational drug (21 CFR 312.8(d)).

## III. QUESTIONS AND ANSWERS

## **General Questions**

Q1: How much time does FDA have to review and respond to a request to charge for an investigational drug?

A1: 21 CFR 312.8 does not specify a timeframe for FDA to respond to a request to charge. However, FDA intends to respond to charging requests within 30 days of receipt when possible.

## Q2: Under 21 CFR 312.8, who must request authorization from FDA to charge for an investigational drug for use under an IND?

A2: Only the sponsor of the IND must request FDA's authorization to charge for an investigational drug for use under the IND (21 CFR 312.8(a)). For example, if the manufacturer of an unapproved drug is not the sponsor of the IND under which the drug will be used, the manufacturer is not required to obtain authorization from FDA to charge the sponsor of the IND for the unapproved drug. However, in such a situation, if the sponsor wants to charge patients to recover the cost charged by the manufacturer, the sponsor must obtain FDA's authorization before it can begin charging patients (21 CFR 312.8(a)(3)).

Q3: Once FDA authorizes a request to charge, who should the sponsor charge?

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A3: Although FDA determines whether a sponsor may charge for an investigational drug used in a clinical trial or expanded access program, FDA does not decide *how* that charging is to be carried out. FDA anticipates that the sponsor would ordinarily charge a patient directly, or would charge a third party payer if reimbursement were available. FDA notes that it has no authority to require that the Centers for Medicare and Medicaid Services (CMS) reimburse for investigational drugs for which FDA has permitted charging. Similarly, FDA has no authority to dictate reimbursement policy to private health insurance providers. For questions pertaining to third party payer reimbursement, CMS or the private insurance company should be consulted.

#### **Charging in Clinical Trials**

## Q4. When a sponsor uses its own investigational drug in a clinical trial, what requirements must the sponsor satisfy to charge for the drug?

A4: When a sponsor is using its own investigational drug, including an investigational use of its approved drug, in a clinical trial, a sponsor must do all of the following to obtain authorization to charge for the drug:

• Provide evidence to FDA that the drug has a potential clinical benefit that, if demonstrated in clinical investigations, would provide a significant advantage over available therapies (21 CFR 312.8(b)(1)(i)),

• Demonstrate that the data to be obtained from the clinical trial are essential to establishing the drug is effective or safe for the purpose of obtaining initial approval, or would support a significant change in the labeling of an approved drug (e.g., a new indication, inclusion of comparative safety information) (21 CFR 312.8(b)(1)(ii)),

 • Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor (21 CFR 312.8(b)(1)(iii)), and

• In its charging request submission, provide documentation to show that its calculation of the amount to be charged is consistent with the requirements of 21 CFR 312.8(d)(1). The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculation (21 CFR 312.8(d)(3)).

Sponsors must meet these requirements and obtain written authorization to charge from FDA before they begin to charge for an investigational drug (21 CFR 312.8(a)(3)).

## Q5: What constitutes extraordinary cost?

A6: As noted above, 21 CFR 312.8(b)(1)(iii) requires that the sponsor demonstrate that it could not conduct the clinical trial without charging for the investigational drug because the cost of the drug is extraordinary to the sponsor. 21 CFR 312.8(b)(1)(iii) also describes reasons why the cost of a drug may be extraordinary. The cost of a drug may be considered extraordinary to a sponsor because of manufacturing complexity, scarcity

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of a natural resource, the large quantity of drug needed because of the size or duration of
the trial, or some other combination of these or other extraordinary circumstances.

Q6: Does FDA consider the financial resources available to a sponsor when determining whether the cost of providing its investigational drug in a clinical trial is extraordinary?

A5: Yes. 21 CFR 312.8(b)(1)(iii) describes reasons why the cost of a drug might be extraordinary *to the sponsor*, including the resources available to a sponsor. For example, a cost that is considered extraordinary to a small, start-up company may not be considered extraordinary to a large, established company.

Q7: When a company is the sponsor of a clinical trial evaluating an unapproved use of its approved drug, is the company required to obtain authorization to charge for its drug?

A7: Yes. In accordance with 21 CFR 312.8(b)(1), a sponsor of a clinical trial must obtain authorization to charge for its own drug, including investigational uses of its approved drug.

Q8: If a sponsor (e.g., a physician-researcher who is a sponsor-investigator) purchases an approved drug from the company that markets the drug or another commercial distribution entity (e.g., a pharmacy, or a wholesaler), for use in a clinical trial, is the sponsor required to obtain authorization from FDA to charge for the approved drug?

A8: No. If a sponsor is not the company that markets the approved drug and must purchase the approved drug for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, or for use of the approved drug as an active control) or as concomitant therapy, the sponsor is not required to obtain FDA authorization to charge for the approved drug (see 21 CFR 312.8(a)(1)).

Q9: If a sponsor's own approved drug is used as concomitant therapy for an approved use during a clinical trial intended to evaluate another drug, should the sponsor obtain authorization to charge for the drug used as concomitant therapy?

A9: In many clinical trials, approved drugs are used as concomitant therapy for subjects during the trials, but are not part of the clinical trial evaluation. For example, patients may be required by a protocol to take certain approved drugs as concomitant therapy before or during the trial to mitigate potential risks of participation in the trial (e.g., antihistamines for immune response concerns in a clinical trial to study a recombinant protein), or may be permitted by the protocol to continue taking certain approved drugs as concomitant therapy during the trial because such drugs are not likely to interact with the study drug(s) or otherwise confound the results of the trial (e.g., pain medications for patients in a clinical trial to study a drug intended to treat cancer), or because discontinuing the drug might adversely affect the patient.

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In accordance with 21 CFR 312.8(b)(1), a sponsor must obtain prior authorization from FDA to charge for its investigational drugs, including investigational uses of its approved drugs. However, FDA does not expect a sponsor to obtain prior authorization to charge for its own approved drug when that drug is used as concomitant therapy for an approved use.

# Q10: How can a sponsor charge for its investigational drug in a blinded, controlled, clinical trial without compromising the blind and, therefore, the integrity of the clinical data generated from the trial?

A10: FDA recognizes that, in certain situations, charging for an investigational drug in a clinical trial may have the potential to compromise the blinding of study subjects to which therapy they have received (e.g., in a situation in which subjects who are in the treatment arm of the study are charged, and subjects who are in the control arm are not charged). However, FDA believes that there are methods for preserving the blind that sponsors could use in most cases. We are not providing hypothetical examples because we anticipate that the method for preserving the blind will be unique to each study design. When these situations arise, the sponsor may seek advice from the appropriate Office of New Drugs (OND) review division on how to preserve the blind, based on the specifics of the given situation.

## Q11: How long may a sponsor charge for an investigational drug in a clinical trial, after FDA authorizes the charging?

A11: Charging may continue for the entire length of the clinical trial, unless FDA specifies a shorter duration (21 CFR 312.8(b)(2)).

#### Charging For Expanded Access Use

## Q12: What requirements must a sponsor satisfy to charge for expanded access to an investigational drug?<sup>4</sup>

A12: The sponsor of an expanded access program must do all of the following to obtain authorization to charge for the drug:

• Provide FDA reasonable assurance that charging will not interfere with drug development (21 CFR 312.8(c)(1)), and;

• In its charging request submission, provide documentation to show that its calculation of the amount to be charged is consistent with the requirements of 21 CFR 312.8(d).

<sup>&</sup>lt;sup>4</sup> The regulations regarding expanded access to investigational drugs for treatment use are at 21 CFR part 312, subpart I. As explained in footnote 3, FDA's draft guidance for industry entitled *Expanded Access to Investigational Drugs for Treatment Use: Qs & As* provides information on expanded access. Once finalized, that document will represent the Agency's current thinking on this topic.

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212 213	The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculation (21 CFR 312.8(d)(3)).
214	For expanded access under 21 CFR 312.320 (treatment IND or treatment protocol), the
215	reasonable assurance that charging will not interfere with drug development must
216	include: evidence of sufficient enrollment in any ongoing clinical trials needed for
217	marketing approval to reasonably assure FDA that the trial(s) will be successfully
218	completed as planned; evidence of adequate progress in the development of the drug for
219	marketing approval, and; information submitted under the general investigational plan
220	specifying the drug development milestones the sponsor plans to meet in the next year
221	(21 CFR 312.8(c)(2)).
222	Expanded access sponsors must meet these requirements and obtain written authorization

## Q13: How long may a sponsor charge for an investigational drug used in an expanded access program, after FDA authorizes the charging?

A13: Charging for expanded access to an investigational drug may continue for one year from the time of FDA authorization, unless FDA specifies a shorter period (21 CFR 312.8(d)(4)). FDA periodically reassesses whether charging is interfering with development of a drug for marketing, and believes that the one-year anniversary is typically a reasonable point in time to re-evaluate charging requests. FDA may reauthorize charging for an expanded access use for additional periods.

from FDA before they begin to charge for an investigational drug (21 CFR 312.8(a)(3)).

# Q14: What must a sponsor do to obtain authorization to continue charging for expanded access to an investigational drug, beyond the duration of its existing charging authorization (i.e., for additional periods)?

A14: If a sponsor wishes to continue charging beyond the duration of its existing charging authorization, the sponsor must submit a request to FDA for reauthorization to charge for the drug (21 CFR 312.8(c)(4)). The request must satisfy the same requirements that the initial request for charging authorization did (see Q12 above). It is also helpful for sponsors to specify whether any information from the original or previous request has changed. The sponsor must receive written reauthorization from FDA, before it can continue to charge for the investigational drug beyond the period previously authorized (21 CFR 312.8(a)(3)).

## Cost Recovery Calculations

## Q15: What costs can a sponsor recover when charging for an investigational drug in a clinical trial?

A15: A sponsor can only recover the direct costs of making a drug available to subjects in a clinical trial — that is, those costs that are specifically and exclusively attributable to providing the drug to clinical trial subjects (21 CFR 312.8(d)(1)). These include costs to manufacture the drug in the quantity needed to conduct the clinical trial for which

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charging has been authorized or costs to acquire the drug from another source, and costs to ship and handle (e.g., store) the drug.

Q16: What costs can a sponsor recover when charging for an investigational drug for expanded access use under 21 CFR part 312, subpart I?

A16: When charging for individual patient expanded access (under 21 CFR 312.310) to an investigational drug, a sponsor may recover only its direct costs associated with making the drug available to the patient (i.e., the costs described in Q15) (see 21 CFR 312.8(d)). When charging for an investigational drug used in an intermediate-size patient population expanded access program (under 21 CFR 312.315) or a treatment IND or protocol (under 21 CFR 312.320), in addition to the direct drug costs, a sponsor may recover the cost of monitoring the access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access use (21 CFR 312.8(d)(2)).

Q17. May the sponsor an expanded access program recover the cost of the fees the sponsors pays to a third party for administering an intermediate-size patient population expanded access program or a treatment IND or protocol?

Yes. FDA interprets 21 CFR 312.8(d)(2) as permitting the sponsor of an expanded access program to recover the cost of the fees paid to a third party for administering an intermediate-size patient population or treatment IND or protocol, including any profit for the third party that may be included in the fees. The fees paid to the third party should be included in the calculation for cost recovery that the sponsor provides in its request to charge.

Q18. Does a sponsor need FDA authorization to charge for the costs of drug delivery, including the costs associated with formulation, packaging, instrumentation, monitoring, disposables, setup, and nursing care?

A18. No. Section 312.8(d)(1) is intended to permit a sponsor to recover the direct costs incurred in making a drug available from the onset of manufacturing to the point it arrives at the destination to which it was shipped or, for a drug acquired from another source as a finished product (e.g., where manufacturing is outsourced), acquisition, shipping, and handling costs for the drug. Recovery of subsequent costs incurred at a clinical trial site (e.g., a hospital or clinic), including pharmacy costs (e.g., the cost to reconstitute a drug for infusion), nursing costs (e.g., costs associated with administering a drug and monitoring study subjects), equipment costs (e.g., intravenous (IV) administration sets, infusion pumps), and costs for study-related procedures (e.g., chemistry labs, radiographic procedures), do not fall within the scope of 21 CFR 312.8. In other words, FDA authorization is not needed to recover those costs.

Q19: What information is a sponsor required to submit to support its cost calculation?

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302	A19: Under 21 CFR 312.8(d)(3), to support its calculation of recoverable costs, a
303	sponsor must provide documentation to show that its calculation is consistent with the
304	requirements of 21 CFR 312.8(d)(1), describing recovery of direct costs, and, if
305	applicable, the requirements of 21 CFR 312.8(d)(2), describing certain additional costs
306	that may be recovered for intermediate-size patient population expanded access uses, or
307	treatment INDs or protocols. This documentation must be accompanied by a statement
308	that an independent, certified public accountant has reviewed and approved the
309	calculations (21 CFR 312.8(d)(3).

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## Q20: Who is an independent, certified public accountant?

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A20: An independent, certified public accountant is a certified public accountant who is not an employee of the company seeking to charge for an investigational drug.